

CYTOP[®] 340

Tributylphosphine [CAS: 998-40-3]

Application 326: Tributylphosphine/Staudinger Reaction

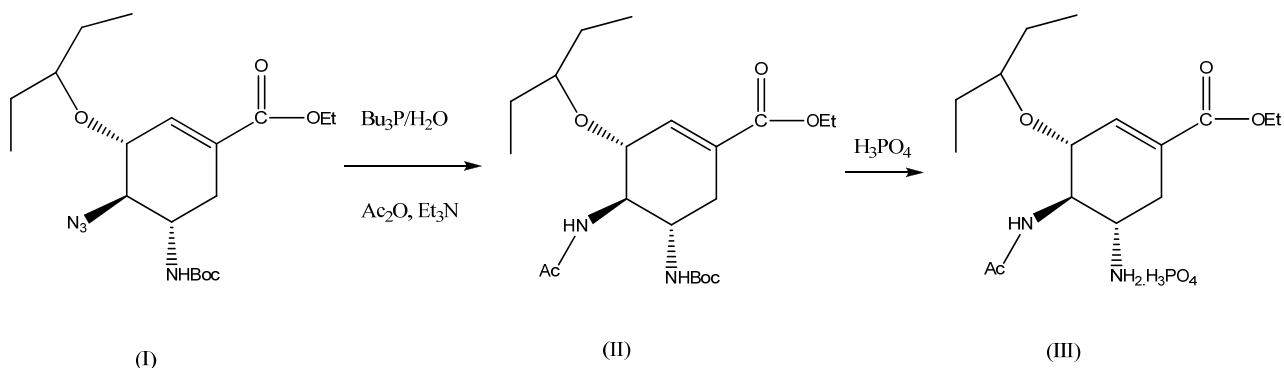
The well known Staudinger reaction is an important enantioselective route to chiral amines. Zutter et al⁽¹⁾ recently reported an efficient route to well known anti-viral oseltamivir starting from relatively inexpensive 2,6-dimethoxyphenol.

In a multi-step process, they achieved an overall yield of 30% of the pro drug oseltamivir phosphate. An enantiomerically pure ethyl ester intermediate was converted via the corresponding triflate with complete inversion to an azide (I). The Staudinger reaction using tributylphosphine was then employed to convert the azide to an amine with complete retention of configuration. This was followed by acetylation to form the precursor (II). On treatment with phosphoric acid in 83% EtOH, the protecting

group was removed with the formation of oseltamivir phosphate (III).

While on a laboratory scale, manipulating tributylphosphine in an inert atmosphere to avoid air oxidation may be a tedious chore, once a process is scaled up to a pilot or full commercial operation, the transfer of tributylphosphine via a liquid discharge port directly from returnable cylinders using a modest nitrogen pressure makes the charging a trivial matter.

The difficulties from handling solid Ph_3P and the subsequent solid and generally insoluble $\text{Ph}_3\text{P}(\text{O})$ byproduct are alleviated.



1) *J. Org. Chem.* 2008,73,4895-4902